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EDITORIAL COMMENT

The Red Devil Revisited*

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Doxorubicin, or "the red devil," as patients affectionately call it because of its color as it flows through their intravenous catheters, is without a doubt one of the most widely prescribed and effective cytotoxic drugs, used in the treatment of cancer. However, its use has been limited by its cardiac toxicity.

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When I went to medical school, I was taught that conceptually, the toxicity of doxorubicin and anthracyclines in general could be compared with that of acetaminophen, such that as long as I operated within "the safe dose," patients with cancer would derive only benefits, not toxicity. I do not believe that my teachers are to be blamed for this thinking. If we take a look at the original von Hoff curve, published in 1979, although there is a continuum of increasing probability of congestive heart failure, the slope of the curve remained relatively flat until the cumulative dose exceeded 550 mg/m^2. Von Hoff et al. (1) reported an overall incidence of heart failure of 2.2%. With the concern that this incidence was not an accurate reflection of the real severity of this adverse event, further work was done by Swain et al. (2). They indeed found a higher overall incidence of heart failure of 5.1%. The estimated cumulative percent of patients was 5% at a cumulative dose of 400 mg/m^2, rising more dramatically to 26% at a dose of 550 mg/m^2. In the curve redrawn by those investigators, the slope of the curve appeared to change at 450 mg/m^2, with the majority of events occurring at cumulative doses exceeding 500 mg/m^2. Their curve and the Von Hoff et al. (1) curve were almost superimposable and, again, essentially flat at low cumulative doses in the range of 100 to 300 mg/m^2, at which heart failure was unusual. As a result , oncologists have felt "relatively safe" during the past 10 years administering anthracycline-based regimens at these low doses.

In this issue of *iJACC*, Drafts et al. (3) report their work using noninvasive imaging to detect evidence of subclinical cardiovascular disease in patients treated with low to moderate doses of anthracycline-based chemotherapeutic agents (50 to 375 mg/m^2). They fill a knowledge gap, as very little is known in terms of what actually happens in the hearts of patients treated with these low doses.

Using cardiac magnetic resonance, the gold standard for left ventricular (LV) volumes, and left ventricular ejection fraction (LVEF) measurement, Drafts et al. (3) found that LV end-diastolic volume remained unchanged throughout therapy. LVEF decreased, and as a result, end-systolic volume increased. The decline in LVEF was paralleled by worsening of midwall circumferential strain. Although decision making in cardio-oncology is very sensitive, and always based on the risk/benefit ratio, it is important to note that anthracyclines were actually started in 6 patients (11%) with mild LV dysfunction (LVEF <50% at baseline). Excluding these patients, an unexpectedly large percent of participants (26%) had developed mild LV dysfunction (LVEF <50%) at 6-month follow-up after the end of therapy. The same percent of patients in this cohort exhibited evidence of subclinical myocardial injury, as demonstrated by elevations of troponins, before the administration of the last dose of anthracyclines. Brain natriuretic peptide levels did not increase. The investigators' findings are consistent with the biomechanical model proposed by Mann and Bristow (4). In this case, the index event is the administration of anthracyclines. Recent work by Zhang et al. (5) indicates that doxorubicin induces

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deoxyribonucleic acid (DNA) double-strand breaks and transcriptome changes through the formation of ternary complexes (Top2-doxorubicin-DNA cleavage complex). The end result is apoptosis of the cardiac myocytes (verified by the elevations in troponins). As cardiac mass is lost, systolic function suffers early (prevalent reductions in LVEF and circumferential strain at 6 months). Despite the reduction in systolic performance, filling pressures remained normal (normal brain natriuretic peptide levels).

To further understand the injury, Drafts et al. (3) also performed late gadolinium enhancement imaging. Excluding the patients with prior myocardial infarctions and revascularization who exhibited findings consistent with myocardial scar, all other baseline and 6-month studies were unremarkable. These findings contradict the pathologic examinations, in which apoptosis is accompanied by myocardial fibrosis (MF) in patients treated with anthracyclines (6). It is unclear if this is a consequence of the short follow-up available in this study or a limitation of the technique used to detect the MF. Late gadolinium enhancement requires normal reference myocardium. Anthracycline-induced cardiomyopathy may induce diffuse myocardial involvement, leaving no normal background myocardium to be used for reference. A new cardiac magnetic resonance–based technique has been used in which the measurement of myocardial T1 provides a quantitative measure of the extracellular volume, most likely reflecting the pathologic extent of MF (7). In a recent study by Neilan et al. (8), extracellular volume was elevated in anthracycline-treated patients compared with age-matched and sex-matched controls, suggesting the presence of MF. Although MF is the most likely cause of the extracellular matrix expansion, other conditions such as edema and infiltration could not be excluded. It is also important to realize that the patients evaluated by Neilan et al. (8) presented much later after receiving their anthracycline-based regimens (a median of 84 months).

From the mechanistic standpoint, the investigators also open our eyes with a new finding. Participants exhibited increases in thoracic aortic pulse-wave velocity, a measure of aortic stiffening. Previous work by Crone et al. (9) illustrated in an animal model the effect of afterload increase in a model of trastuzumab-based cardiotoxicity using a knockout model. This finding reminds us of the importance of ventriculoarterial coupling and emphasizes the importance of understanding the heart as part of an integrated cardiovascular system and not in isolation.

The most important question to ask is how we fit this piece of data into the big picture.

New "real-world" and Medicare data confirm the rate of heart failure in patients receiving anthracyclines at about 5%, as previously described by Swain et al. (10,11). It is unclear to me who among the 26% of patients with reduced LVEFs at the 6-month follow-up reported in this study will improve, who will stay the same, and who will progress to be part of the 5% of patients who actually develop heart failure syndrome. I believe that further work needs to be done to understand the potential role of myocardial inflammation and fibrosis in the risk stratification of these patients and the optimal method to identify it.

The investigators also measured the effect of anthracyclines on the quality of life, finding a negative impact over time. Although interesting, I am not sure what is to be blamed for the perceived deterioration in the quality of life: the cancer, the chemotherapy, or its well-recognized profile of side effects. It would be intuitive to expect a worse perception of quality of life in patients who develop cardiotoxicity. Although the investigators observed a trend in this direction, it did not prove to be of statistical significance.

I propose looking at the findings of this study not as a glass half empty but as a glass half full. Being aware that anthracyclines at low doses are not "innocent" and are actually associated with a rate of early LV dysfunction much higher than anticipated gives us the option of reacting with a strategy of aggressive surveillance and treatment of cardiotoxicity. On the bright side, recent work by Cardinale et al. (12) has challenged the concept of the "irreversibility of anthracycline-induced cardiomyopathy." Their data demonstrate that the condition is potentially reversible, as long as it is recognized early. We can then integrate the findings of the present study, hypothesizing that the development of heart failure may be potentially prevented in these patients if heart failure therapy is started at a point at which, just as in this group of patients, end-diastolic volume is still normal and LV remodeling has not occurred. As a result, it becomes of paramount importance to follow the LV dimensions and systolic function of these patients during and immediately after therapy and to do so using sensitive techniques, including strain imaging, which would allow very early detection and aggressive treatment of cardiotoxicity, hopefully at a point at which the LVEF has not changed.

Finally, recognizing that cardiac disease indeed represents the most common reason for mortality

among cancer survivors, we are working on changing our model of care for these patients through the creation of cardio-oncology centers of excellence across the nation. Oncologists, prevention specialists, radiologists, and heart failure cardiologists are now making decisions together before, during, and after chemotherapy in a patient-centered model, with the goal of optimizing cancer therapy while minimizing cardiac toxicity.

I am confident that this model, along with elegant contributions to our knowledge such as that of Drafts et al. (3), will give us, through better understanding of the mechanisms of disease, the option of developing treatment strategies that will secure cancer treatment with minimal or no toxicity.

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